55. (new) A method for inhibiting angiogenesis comprising administering to a mammal an effective amount of a compound of the formula X_1-SEQ ID NO:1-X_2 wherein

X_1 is from zero to twelve amino acids, and

X_2 is from zero to twelve amino acids.

56. (new) A method of inhibiting angiogenesis according to claim 1 wherein

X_1 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:2, or N-terminal truncation fragment thereof containing at least one amino acid, and

X_2 is

(i) zero amino acids, or

(ii) the segment SEQ ID NO:3, or C-terminal truncation fragment thereof containing at least one amino acid.

Remarks

Claims 1-7, 24 and 49-56 are pending in the application. Claims 8, 12-23 and 25-48 have been cancelled without prejudice to the filing of one or more divisional applications. New claims 49-56 find support in original claims 1-7 and 24. Reconsideration is respectfully requested in view of the following remarks.

Applicants appreciate Examiner's reconsideration of the restriction requirement and confirmation that claims 6 and 7 are properly grouped within elected Group I.

The rejection alleges that the application currently names joint inventors. This is incorrect. Keith R. McCrae is the sole inventor.

Response to Section 102 Rejection of Claims 1-7 Over Auerswald

Claims 1-7 are rejected under 35 U.S.C. 102 as allegedly anticipated by Auerswald *et al* ("Auerswald"). The rejection alleges that Auerswald teaches the sequences contain in SEQ ID NOS: 1-4, 9 and 10. The rejection alleges that although the "sequences" disclosed by Auerswald "exceed 12 amino acid residues, the claims recite open language such as 'comprising' and 'has'". Thus, the rejection concludes that the reference sequence is identical to the claimed sequences.

Auerswald discloses, in pertinent part, a 125-amino acid recombinant peptide corresponding to human kininogen (HK) amino acids G253-S377 (according to Auerswald's numbering). The peptide is designated as "ANSM kininogen". This peptide includes the entire HK domain 3.

Claims 1-7 are not anticipated by Auerswald. Claim 1 defines a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the formula X_1-SEQ ID NO:1-X_2, wherein X_1 and X_2 are each from zero to twelve amino acids. SEQ ID NO:1 is Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys, which corresponds to the portion of HK domain 3 spanning HK amino acids Asn(275) to Lys(282) (according to applicant's numbering). Assuming that X_1 and X_2 each duplicate the twelve amino acid segments flanking SEQ ID NO:1 in the HK native sequence, the largest claimed peptide duplicating the HK native sequence is the 32-amino acid peptide Thr(263)-Val(294) (according to applicant's numbering). Auerswald does not teach or suggest a pharmaceutical composition of such a peptide.

It is respectfully submitted that the anticipation rejection is based upon a misreading of claim 1. The formula X_1-SEQ ID NO:1-X_2 is not open-ended to embrace pharmaceutical compositions containing peptides larger than 32 amino acids. While the open-ended transition word "comprising" is present, the word appears in the preamble of the claim, linking the two elements of the claimed pharmaceutical composition - "a pharmaceutically acceptable carrier" and "a compound of the formula X_1-SEQ ID NO:1-X_2". The "comprising" preamble word opens the claimed composition to other ingredients in the pharmaceutical composition. The "comprising" word does not open the scope of the *compound contained within the composition* to compounds that are not within the formula X_1-SEQ ID NO:1-X_2.

Examiner alleges that the word "has" somehow opens claim 1 to an interpretation that embraces Auerswald's ANSM kininogen. The word "has" does not even appear in claim 1. While "has" appears in dependent claims 4-7, these claims can not be any broader with respect to the scope of compound than the compound as defined in claim 1, i.e., X_1-SEQ ID NO:1-X_2. Thus, the presence of the word "has" in the dependent claims does not cause the claims to read on the ANSM kininogen of Auerswald.

It is noted that Auerswald generated tryptic peptides from ANSM kininogen. The fragments were isolated and identified by partial sequencing. Even assuming *arguendo* that a tryptic peptide of Auerswald's ANSM kininogen could be considered to fall within the scope of X_1-SEQ ID NO:1-X_2, the peptide would not anticipate the claimed invention. None of the tryptic fragments were combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition. None of the tryptic fragments were tested by Auerswald for biological activity. No biological activity or pharmaceutical activity is predicted by Auerswald. The tryptic peptide were generated merely to confirm the primary structure of recombinant ANSM. Thus, Auerswald does not teach or suggest the claimed pharmaceutical composition defined by claim 1. Claim 1 is not anticipated by Auerswald.

Claims 2-7 recite additional features of the claimed pharmaceutical composition. Since claim 1 is not anticipated by Auerswald, claims 2-7 are likewise novel.

Response to Section 103 Rejection of Claims 1-7 and 24 Over Auerswald

Claims 1-7 and 24 have been rejected as being allegedly obvious over Auerswald. As discussed above, claims 1-7 are directed to pharmaceutical compositions of peptides of the formula X_1-SEQ ID NO:1-X_2. Claim 24 is directed to a method of treating angiogenesis, comprising administering a composition according to claim 1. While claims 1-7 are included in the rejection, the *only* reasons given for obviousness are focused on a method of inhibiting angiogenesis, which is the invention of claim 24. Thus, while the Section 103 rejection on its face refers to "Claims 1-7 and 24", the rejection is supported only be reasoning directed to claim 24. However, in abundance of caution, and to protect the record for purposes of appeal, applicant responds to the rejection of claims 1-7 as obvious over Auerswald.

As indicated above, claims 1-7 define a pharmaceutical composition of peptides of the formula X_1-SEQ ID NO:1-X_2. Auerswald discloses the 125-amino acid recombinant peptide "ANSM kininogen" corresponding to human kininogen (HK) amino acids G253-S377 (according to Auerswald's numbering). The largest peptide according to applicant's formula X_1-SEQ ID NO:1-X_2 has 32 amino acids. Auerswald measured the inhibitory activity of ANSM kininogen against certain cysteine proteinases. No pharmaceutical composition comprising ANSM kininogen is disclosed. It would not have been obvious to one of ordinary skill in the art, at the time the invention was made, to combine ANSM kininogen with a pharmaceutically acceptable carrier. No pharmaceutical utility for ANSM kininogen is disclosed. Nothing in the disclosure of Auerswald provides inventive or motivation for preparing a pharmaceutical composition of ANSM kininogen.

Moreover, even assuming arguendo that one of ordinary skill in the art would be motivated to combine ANSM kininogen with a pharmaceutically acceptable carrier, the result is not the claimed invention. For the reasons set forth above, ANSM kininogen is not a peptide within the formula X_1-SEQ ID NO:1-X_2.

Furthermore, there is no incentive or motivation provided by Auerswald to prepare pharmaceutical compositions from any tryptic peptide of ANSM kininogen. As indicated above, none of the tryptic fragments were tested by Auerswald for biological activity. The tryptic peptides were generated merely to confirm the primary structure of recombinant ANSM. No biological activity or pharmaceutical activity is predicted by Auerswald. There is nothing in the disclosure of Auerswald to motivate the preparation of a pharmaceutical composition of any ANSM kininogen tryptic peptide. The pharmaceutical composition of claims 1-7 would not have been obvious at the time the invention was made in view of the disclosure of Auerswald.

Claim 24 defines a method of inhibiting angiogenesis comprising administering to an individual an effective amount of the composition of claim 1. In view of the nonobviousness of the claim 1 composition, the method of claim 24 is also nonobvious. "[P]roper claim construction requires treating language in a process claim which recites the making *or using* of a

nonobvious product as a material limitation." *MPEP 2116.01 (emphasis added).* The same is true of new claims 49-54.

The rejection admits that Auerswald fails to teach a method of inhibiting angiogenesis comprising administering "the peptide disclosed". It is assumed that by "the peptide disclosed" is meant ANSM kininogen. Examiner further alleges (incorrectly, for the reasons set forth above) that Auerswald teaches peptides "with a 100% sequence identity" to peptides of the present invention. Next, after admitting that Auerswald fails to teach a method of inhibiting angiogenesis, *Examiner turns to applicant's disclosure to provide the missing teaching!* Examiner writes:

> "Auerswald teaches the claimed peptides with a 100% sequence identity which are described in the instant specification as possessing anti-angiogenic activity (see page 4 of the specification).

Page 4 of the specification sets forth the amino acid sequence of HK domain 3, and a brief discussion of certain prior art references directed to studies on HK domain 3. None of the referenced prior art pertain to inhibition of angiogenesis. The only teaching at page 4 regarding inhibition of angiogenesis is the statement of *applicant's invention* at lines 24-25: "The compounds of the present invention are in the form of peptides which possesses anti-angiogenic activity." Thus, Examiner has used *applicant's own specification*, not the prior art, to reject claims directed to applicant's invention. With all due respect, this is highly improper.. Examiner is reminded of the mandate of MPEP 706.02(j): "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art **and not based on applicant's own disclosure**." (emphasis added)

The rejection proceeds with the following misstatement of the teachings of Auerswald:

> "In addition, the reference provides motivation to obtain a method to inhibit angiogenesis."

"Motivation to obtain" is irrelevant to a correct analysis under Section 103. Examiner's attention is again directed to MPEP 706.02(j) for the contents of a proper Section 103 rejection. Moreover, the word "angiogenesis" does not appear anywhere in the disclosure of Auerswald.

Indeed, Examiner admits that Auerswald does not teach a method of inhibiting angiogenesis. If Auerswald does not teach a method of inhibiting angiogenesis, how then can that reference possible motivate such a method? Clearly, Auerswald provides not motivation for a method for inhibiting angiogenesis.

The rejection proceeds with the following curious statement of the alleged teaching of Auerswald, which is entirely correct, to the extent the statement is understood:

"Auerswald teach that there is a structure function relationship with the disclosed peptides..."

The only "structure" disclosed by Auerswald is ANSM kininogen. The only function disclosed by Auerswald is ANSM kininogen inhibition of certain cysteine proteinases. With only one structure, it is not seen how a trend in function is established by Auerswald. Even if a trend is established by the single compound, ANSM kininogen, the only function of that compound disclosed by Auerswald is inhibition of cysteine proteinase activity, not inhibition of angiogenesis. Even assuming *arguendo* that Auerswald discloses a structure-function relationship (which is not admitted), any such relationship is directed to inhibition of cysteine proteinase activity, which is irrelevant to the claimed invention.

The rejection continues:

> "...once in possession of the anti-angiogenic peptides, the method is an obvious extension."

For the reasons stated above, the prior art (i.e., Auerswald) was not in possession of "the anti-angiogenic peptides", assuming that Examiner means the peptides of the formula X_1-SEQ ID NO:1-X_2. Applicant is at a loss, however, to comprehend the meaning of "the method is an obvious extension". What is the *thing* which is so obviously extended into the claimed method of inhibiting angiogenesis? It appears that Examiner is again violating the mandate of MPEP 706.02(j) by drawing the suggestion to make the claimed invention from applicant's own disclosure of anti-angiogenic activity of the peptides of the formula X_1-SEQ ID NO:1-X_2.

The rejection continues:

"Additionally, it is well known in the art that peptides derived from Kininogen can inhibit angiogenesis. Therefore, the claimed invention as a whole was *prima facie* obvious.

Examiner has provided no supporting evidence for this assertion of prior art knowledge. Examiner may take official notice of facts outside of the record only when those facts are "capable of instant and unquestionable demonstration". MPEP 2144.03. When an applicant traverses an assertion of prior art knowledge, the examiner must cite a reference to support his/her position. MPEP 2144.03. Applicant hereby traverses Examiner's assertion of prior art knowledge that peptides derived from kininogen inhibit angiogenesis. Further, a demand for such evidence is hereby made pursuant to MEPE 2144.03. Applicant reserves a complete response to this point until the appropriate evidence is provided by Examiner.[1]

For the reasons set forth above, the claimed inventions as defined in claims 1-7 and 24-56 are not obvious in view of Auerswald.

Response to Section 103 Rejection of Claims 1-7 and 24 Over Auerswald in view of Colman

Claims 1-7 and 24 have been rejected as allegedly unpatentable over Auerswald taken with Colman. While claims 1-7 are included in the rejection, the *only* reasons given for obviousness are focused on a method of inhibiting angiogenesis, which is the invention of claim 24. Thus, while the Section 103 rejection on its face refers to "Claims 1-7 and 24", the rejection is supported only be reasoning directed to claim 24.

The rejection alleges that Auerswald teaches "peptides that are identical to the claimed invention which are disclosed as being anti-angiogenic". Applicant again respectfully points out that (1) the ANSM kininogen is not a compound of the formula X_1-SEQ ID NO:1-X_2, and (2) the anti-angiogenic activity of the formula X_1-SEQ ID NO:1-X_2 peptides in the specification is applicant's own teaching *of the invention.* It is improper to use the specification's teachings of the invention in a rejection.

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[1] In the final section of the office action, Examiner asserts Colman *et al., Blood* ***92***, No. 10), Supl 1 (Part 1 of 2) , Abstr. #701. But Colman is directed to peptides of HK domain 5, not domain 3, and cannot therefore support the rejection.

After correctly admitting that Colman *et al.* do not teach the formula X_1-SEQ ID NO:1-X_2 peptides, the rejection then mischaracterizes the Colman reference as teaching "the same domain as claimed" by applicant. First, applicant does not claim a "domain", but rather a pharmaeuctical composition comprising peptides which may be modeled from a specific portion of a specific domain of HK. Second, that domain is not domain 5 as described by Colman, but rather domain 3. HK domain 3 consists of HK amino acids Gly(235)-Met(357) (specification, page 4). As indicated by Colman, domain 5 consists of HK peptides Lys(420)-Ser(513). The two domains are entirely distinct, non-overlapping regions of the kininogen molecule.

Examiner makes the following statement in furtherance of the rejection:

> "For example, page 7 of the instant specification disclose that the invention is directed to peptide fragments of the HK domain 3, which fragments inhibit endothelial cell proliferation and thus possess anti-angiogenic activity".

It appears that Examiner is again violating the mandate of MPEP 706.02(j) by drawing the suggestion to make the claimed invention from applicant's own disclosure of anti-angiogenic activity of the peptides of the formula X_1-SEQ ID NO:1-X_2.

Examiner remarks that Colman teaches that "HKa is proangiogenic and that peptides from HKa could complete and inhibit angiogenesis by inhibiting interaction of HKa with uPAR." Examiner alleges that one of ordinary skill in the art would thus be motivated to combine the teachings of Auerswald and Colman,

> "because both references teach peptides derived from Kininogen and Colman et al. teach a method of inhibition of angiogenesis with ***said peptide***" (emphasis added).

Examiner concludes that the invention was obvious to make and use the invention from the combined teachings of Auerswald and Colman.

In the statement quoted above, what does Examiner mean by "said peptide"? It seems that Examiner is laboring under the misconception that Auerswald and Colman describe the same peptide. Auerswald's ANSM kininogen is a 125-amino acid recombinant peptide corresponding to the entire HK domain 3. Colman discloses a recombinant polypeptide corresponding to the entire HK domain 5 (Lys420-Ser513), and a fragment thereof including

amino acids Lys420 to Asp474. The bridge which Examiner has constructed between these references to force their combination, that they teach the same peptide, is completely false. Colman's teachings are limited to these specific peptides from domain 5. There is not a single mention by Colman of any other kininogen domain, let alone domain 3. There is no teaching or suggestion in Colman that peptides from other HK domains could be anti-angiogenic.

It is only with hindsight and the benefit of applicant's disclosure that one would combine the disparate teachings of Auerswald and Colman, which are directed to two entirely different, non-contiguous domains of the kininogen molecule. There is nothing at all in the asserted references to suggest that Auerswald's ANSM kininogen, which constitutes the entirely of HK domain 3, has any anti-angiogenic properties. Indeed, the only teaching of anti-angiogenic peptides from domain 3 is applicant's own specification, from which Examiner freely quotes in constructing the various rejections traversed herein.

Even assuming the combination of references is proper, which it is not, the resultant is not the claimed invention. For the reasons set forth above, Auerswald's ANSM kininogen is not an X_1-SEQ ID NO:1-X_2 peptide of applicant's claimed composition and method.

Claims 1-7, 24 and 49-56 are not unpatentable in view of the combination of Auerswald and Colman.

In conclusion, applicant respectfully submits that the claims remaining in the application are in condition for allowance. An early notice of allowance is earnestly solicited.

Respectfully submitted,

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APPENDIX A

MAR-UP OF AMENDED CLAIM

1. (twice amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the formula X_1-SEQ ID NO:1-X_2 wherein

X_1 is from zero to twelve amino acids, and

X_2 is from zero to twelve amino acids[,]_.